Prior to initiating the testing of a substance, an NIEHS/NTP staff scientist develops a research concept document. This research concept outlines the general elements for a program of study of the substance to address specific research needs raised in its nomination to the testing program. Additional information about the nomination, review, and selection of substances for study by the NTP is provided from *Nominations to the NTP Testing Program* (http://ntp.niehs.nih.gov/go/nom).

NTP Concept Document: Perfluorinated Compounds Class Study

The US EPA nominated to the NTP a class study of potential health effects of perfluorinated compounds (PFCs). The nominated compounds include perfluoroalkyl sulfonates (C6, C9, C10, C12), perfluoroalkyl carboxylates (C6, C8, C9, C10, C12), and two telomer alcohols (8+2, 10+2). Perfluorooctanesulfonate (PFOS) and perfluorooctanoate (PFOA), the most widely studied PFCs, are persistent in the environment, do not undergo biotransformation, and are present in the serum of the general US population. EPA's nomination included prechronic range finding studies, pharmacokinetics, modified one-generation reproductive toxicity studies, and a 2-year bioassay of PFOA with in utero exposure. Because the developing organism is the primary target of PFOA and PFOS and because two-generation studies of PFOS and PFOA did not reveal any unique effects in the F2 generation, one-generation repro tox studies of PFCs are appropriate. To assess potential health effects of PFOA from animal toxicity data, EPA proposed a margin-of-exposure approach that is based on comparisons of steady-state serum levels and/or areas under plasma 24-hr concentration curves (AUC) in animals and humans. The proposed NTP studies will take an AUC approach for the selection of doses and will provide doseresponse information that can be used for a cumulative risk assessment or an assessment of the health effects of individual PFCs.

- 1) Pharmacokinetic data will be generated to estimate the internal dosimetry of each compound in the blood and liver of Sprague-Dawley rats. This information, in conjunction with toxicity data, will be used to determine dosing regimens for subsequent comparative oral toxicity studies (e.g., include a common internal dose metric). PFOA and PFOS are readily absorbed after oral or inhalation exposure, but poorly metabolized and cleared. Plasma half-lives of PFCs in rats vary substantially as a function of chain length and differ between males and females. Blood and liver time-course data after iv and gavage administration will be obtained for the C4, C6, C8, and C10 sulfonates, for the C6, C8, and C10 carboxylates, and for the 8+2 telomer. Metabolite data will be needed only for the telomer. Time-course data for parent compound and major telomer metabolites in the fetus, placenta, and in the plasma and liver of the dam will be used to provide estimates of the dosimetry of each compound in the fetus and dam during gestational exposure. The PK work will be conducted as a single comparative study and the data will be used to develop predictive models that describe the PK behavior for these structurally related chemicals.
- 2) In vitro studies can provide data on the potency of cellular and subcellular effects without the need to adjust for differences in elimination kinetics. Four in vitro evaluations were identified for the PFCs: a) mitochondrial toxicity, b) fetal lung growth, c) insulin secretion in isolated pancreatic islets, and d) steroidogenesis in isolated Leydig cells. Relative in vivo toxicities of these chemicals will be predicted based on the combined in vitro data and AUC information. The in vitro studies can be performed through an RO3 grants program.
- 3) 28-day oral toxicity studies will be conducted in male and female Sprague-Dawley rats (beginning at 6 weeks of age) to determine the impact of chain length (C6, C8, C10) on the

toxicity of these chemicals and to compare the relative toxicities of carboxylates versus sulfonates. Endpoints include: mortality, growth, organ weights, histopathology (pathology cut down procedures will be utilized to save costs), aromatase and liver peroxisomal enzyme activities, hematology, clinical chemistry (serum triglycerides, cholesterol, estradiol, testosterone, thyroid hormones, alkaline phosphatase, bile acids, globulin), SMVCE, and terminal plasma and liver concentrations of parent compound.

- 4) Exposures in the developmental toxicity studies in Sprague-Dawley rats will begin in utero (gestation day-6) and continue until 10 weeks of age. In addition to the endpoints in the 28-day studies, evaluations will be made of litter effects (number of live/dead pups, sex ratio, % survival, external malformations), sexual maturation, immunotoxicity, and developmental neurotoxicity.
- 5) Carcinogenicity study of PFOA in Sprague-Dawley rats will begin on GD-6 and continue through 110 weeks of age. A dose group with exposures beginning at 6 weeks of age (traditional approach) will be included to evaluate the impact of in utero exposure on the carcinogenicity of PFOA in male and female rats. Results from this study will be compared to previous studies that did not include in utero exposures.

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